Ultrasonographic Screening for Fetal Malformations

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When operated rigorously at certain periods of gestation, ultrasonography is the best tool to detect fetal malformations. It can show many different types of defects, sometimes very early in pregnancy. The usefulness of the screening process also depends on the technical quality of the scan, the skill of the operator, the competence of the interpreter, and the availability of options regarding malformation management.

The great majority of pregnant women are at low risk for fetal malformation, and a small minority are at high risk (e.g., those with a predisposing genetic history or maternal diabetes). Both low-risk and high-risk groups can carry malformed fetuses, of course, but the numbers and proportions differ. The number of malformations is higher in low-risk gravidas than in high-risk gravidas because most pregnant women belong to the former group. In contrast, the proportion of malformations is higher in high-risk gravidas than in the low-risk group. Regardless, the risk for fetal malformation is always present among pregnant women and suggests a role for routine ultrasonographic screening.

Because of the paucity of symptoms generating suspicion of malformation, ultrasonography is a very valuable tool for detecting anomalies in women whose pregnancies are otherwise uneventful.

Is routine screening for fetal malformations justified?

Screening a specific population sample is justified when the anomaly is present in a significant number of cases and is deleterious; appropriate interventions can be carried out in a timely fashion; and the screening procedure itself is safe, reliable, easily available, and cost-effective.

Is the frequency high enough to merit screening?

Compared with other obstetric and neonatal diseases for which screening is available, fetal malformation is a common complication. The prevalence is as high as 6.5%, but only 2% to 2.5% of these malformations are considered to be potentially life-threatening or to represent major cosmetic defects. Approximately 150,000 children with malformations are born annually in the United States.

Is the outcome of nondetected malformation detrimental enough to warrant screening?

Most fetal malformations exhibit highly deleterious effects on health, occasionally during fetal life but usually after birth. In some cases, harmful outcomes do not appear until childhood or adult life. Similar structural malformations may display a broad spectrum of harmful consequences; it is not always easy to predict short- or long-term outcomes. As a result, some experts question the need for prenatal ultrasound screening. However, in addition to revealing malformations, ultrasonography can identify markers for fetal chromosome defects (e.g., trisomy 21) that would otherwise remain unsuspected because they are not always associated with malformations.

Lethal/incurable malformations. Medicine has not advanced far enough to cure certain neural tube anomalies and heart defects. Death, the expected outcome, occurs soon after birth but occasionally during pregnancy. Infants who do survive are severely handicapped. Diagnosis during pregnancy allows the choice of termination. Serious but curable malformations. Without appropriate management before or immediately after
birth, these malformations (e.g., circulatory or respiratory system anomalies) may be lethal. Urgent care is facilitated by antenatal detection. If inexpertly managed, some infants may escape death only to develop a permanent handicap. Late diagnosis, deficient transport circumstances, and/or inadequate postnatal conditions increase the likelihood of adverse outcomes.

Curable malformations. Although these cases may not necessarily benefit from prenatal diagnosis per se, they are certainly not harmed by it. Current technology enables the detection of approximately 56% of fetal malformations. Subsequent search for abnormal karyotype may change prognosis and management. Chromosomal abnormalities are present in up to 50% of cases of proven cystic hygroma and endocardial cushion defect. Rates of abnormal karyotypes among fetuses exhibiting isolated congenital heart defects, facial clefts, or gastrointestinal (GI) defects are 9%, 8%, and 7%, respectively.

Can prenatal diagnosis of anomalies ease emotional pain?

When obstetric ultrasonography was in its infancy, only the most serious anomalies were detected. Most malformations were lethal or incurable. Finding malformations could only help parents to shorten the tragedy of a hopeless event. Now, many malformations are detectable. Although most do not require urgent treatment, and some require no treatment at all, prenatal diagnosis can still help parents-to-be to prepare themselves emotionally for the challenges to come.

Prenatal ultrasonographic screening benefits both physicians and their patients. It enables OB/GYNs to identify fetal malformations at a stage when they might be curable; at the very least, they will be able to provide parents-to-be with information necessary for decision-making. And, expecting parents will gain knowledge about their child's health, including physical and mental integrity. If findings are negative, their fears about carrying a child with an anomaly will be allayed. The relatively low prevalence of malformations in the general population, coupled with the very low incidence of false-positive results on ultrasound, provides the opportunity to disclose good news to many sets of parents. If screening results are positive, then parents should receive psychological counseling as early as possible: Informed parents are better able to participate in management decisions and have a better approach to the birth. Conversely, insufficient psychological preparation may adversely affect parents' behavior and damage their relationship with the afflicted child.

Studies of parents' psychological reactions to true-positive, false-positive, and false-negative findings show wide variation. Many parents experience more difficulty handling ambiguous findings than "known" abnormalities, however bad. Patients who have experienced false-negative results are more likely to suffer emotionally than are those who receive true-positive findings. Despite the anxiety generated by false-positive findings, parents' attitudes toward ultrasound are generally affirmative once they learn that their child is normal.

Is screening ultrasonography cost-effective?

Few studies have analyzed the cost-effectiveness of screening ultrasonography. It is easy to assess certain costs: For example, the purchase and maintenance of high-quality ultrasound equipment and the use of well-trained operators are expensive. It is impossible to calculate other "costs," however, including parental suffering and grief and the resulting family disorganization. And it is also difficult to assess the effectiveness of prenatal screening ultrasonography because similar sets of anomalies can result in such a wide range of treatments and outcomes. However, one study has shown that one-stage, second-trimester screening is highly cost-effective. Other studies have also addressed this issue.

How does prenatal screening influence infant health?

Prenatal ultrasonographic screening for malformation differs from primary prevention: It cannot prevent activation of the anomaly. However, when it reveals lethal or incurable defects, it gives expecting parents the opportunity to terminate the pregnancy. And if it reveals malformations that are amenable to therapeutic intervention, it can ultimately reduce perinatal morbidity and mortality. In many cases, severe but curable defects (e.g., cardiac malformations) can be managed by treating newborn infants without delay. This is much easier to achieve when it is anticipated that parturients will need to be transported to tertiary perinatal units. Even in nonurgent cases, prenatal detection may be beneficial. For example, early recognition of certain renal anomalies that might otherwise not become apparent until fairly late after birth might avert progressive deterioration of kidney function within the first months of life. Routine and detailed fetal scanning quintuples the detection rate of urinary tract abnormalities before 20 weeks' gestation.
Comparisons between autopsy reports and ultrasound findings show that expertly performed and interpreted scans provide highly accurate information. False-positive findings—at least those severe enough to alter the course of the pregnancy—are extremely rare. Systematic use of "expert ultrasound" after positive findings helps to avoid these errors.

**What are the options after malformation is diagnosed?**

Exercising a particular management option is solely up to the parents. However, they should base their decision on complete information—including ethical aspects—gathered by a team of experts composed of an obstetrician, sonologist, geneticist, neonatologist, surgeon, and psychologist.

Proposed options depend primarily on the severity of the diagnosed anomaly, and include:

- termination of the pregnancy
- intrauterine treatment of the affected fetus
- maternal transport to a tertiary care center
- premature delivery
- instantaneous, highly specific postnatal care
- additional diagnostic procedures to guide postnatal treatment
- initiation of monitoring if immediate treatment is not advisable.

**What are alternatives or adjuncts to ultrasonography?**

Patient history and clinical examination are the first steps in determining whether a fetus might be at risk for malformation. Maternal serum a-fetoprotein (MSAFP) is an efficient marker for neural tube defects (NTDs) and a few other anomalies, but it is not superior to ultrasound performed by trained personnel. False-positive results of this blood test are not unusual, and abnormally high values are not diagnostic. Further, ultrasonography is still necessary to confirm, localize, and size the defect. Even if "triple screening" (measurement of MSAFP, estriol, and human chorionic gonadotropin [hCG]) suggests the presence of trisomy, ultrasonography and karyotyping are still necessary.

Ultrasongraphy has greatly reduced the use of amniocentesis: Twenty percent of cases slated for amniocentesis are canceled after ultrasonographic correction for gestation age. Consequently, ultrasound helps to reduce unjustified fetal losses due to amniocentesis.

Among the many imaging techniques available, ultrasound is the only one used for prenatal screening because of its many advantages: relatively low cost, ease of performance, real-time display, acceptability to patients, and wide availability, including in private offices. More important, the technology is so advanced that comprehensive malformation screening is useful from the late first trimester onward.

**How long does it take?**

Ultrasoundographic examination should follow strict methodology to capture any signs suggestive of malformation, localized anywhere on, inside, or around the fetus. Depending on factors such as image quality, gestational age, and maternal obesity, checked items can be examined within 10 to 30 minutes. The primary screening process stops when all significant structures have been seen as normal. When a malformation is suspected, complementary expert ultrasonography is then employed.

**What can it show?**

In many cases, prenatal ultrasound shows a detailed image of the defect itself. Figures 1 and 2 depict a cleft lip and a hypoplastic left ventricle of the heart, respectively. Spina bifida is another common defect readily seen on ultrasound. In other cases, detection is possible because of image alternations related to fluid collection above strictures (e.g., duodenal atresia, as shown in Figure 3). Some defects are visible at any gestational age, and others are best seen at first- or early second-trimester examination (e.g., nuchal translucency, as shown in Figure 4). Still others are best visualized late in pregnancy (e.g., GI defects).
A malformation is suspected when the expected image of the fetus, or a part of it, is altered because of pathologic changes. Some of these changes are considered "soft" markers for malformation and chromosome anomalies. They do not correspond to a specific malformation but are frequently associated with malformation ("call signs"). Call signs may involve the fetus, the placenta, the cord, or the amniotic fluid. The "banana" sign (Figure 5) and the "lemon" sign correspond to unusual shapes of the cerebellum and skull, respectively, and help to detect nearly all cases of open spina bifida. Other signs, such as nuchal translucency during the first trimester and nuchal thickness during the second trimester, are valuable markers for trisomy 21 or other chromosome anomalies, or they may be precocious signs of cardiovascular anomaly. One-fourth of malformed fetuses have more than one anomaly; thus, any malformation should be considered as a call sign for additional ones.
Other common call signs (e.g., polyhydramnios, oligohydramnios, intrauterine growth retardation [IUGR]), are encountered in 43% of malformation cases. Oligohydramnios during the second trimester is an important sign of fetal anomaly or distress; malformation is present in 50% of cases and is lethal in 90%. Hydrops fetalis, another call sign, is associated with malformation in 57% of cases, and early IUGR with confirmed gestational age is associated with malformation in 10% of cases. Multiple pregnancies have a three-fold higher incidence of fetal malformation. Abnormal fetal heart rate is due to a major anomaly in 20% of affected fetuses. Single umbilical artery (SUA), which is present in 0.6% of normal pregnancies, is considered a malformation only if it coexists with other anomaly. Still, SUA is associated with placental anomalies, increased perinatal mortality, aneuploidy, and severe malformation.

In addition to anatomic defects, ultrasonography can display functional abnormalities. Abnormal patterns of fetal activity--rapid, spasmodic, uncoordinated movements of the extremities or inactivity--may suggest arthrogryposis or muscular or central nervous system anomalies. Arrhythmias are suggestive of heart defects, and vomiting, of GI tract stenosis.

When should it be performed?

Ultrasonographic screening for trisomy 21 during the first trimester was introduced by Nicolaides in 1992. Today, measurement of the clear space visible in the region of fetal neck (nuchal translucency) at 11 to 14 weeks' gestation is routinely determined by ultrasonography. If this space exceeds 2.5 mm in thickness, karyotyping is suggested. This procedure yields a detection rate of 80% (false-positive rate, 5%). By factoring in maternal age and measurement of two biochemical markers (maternal serum free b-hCG and pregnancy-associated plasma protein-A), the detection rate for trisomy 21 rises to 89% (false-positive rate, 5%).

Second-trimester screening is performed between 18 and 22 weeks' gestation. Examination of the quantity of amniotic fluid is important at this stage. Third-trimester screening usually occurs between 30 and 32 weeks' gestation, and is chiefly performed to check fetal growth. However, it is still feasible to detect malformation signs occurring late, particularly those in the heart, GI tract, and urinary tract.

Although it would be ideal to perform ultrasonographic examinations in every gravida on a monthly basis, this is not practical. Instead, it would be useful to have two scans done, one in the first
trimester and one in the second trimester.

**What is the sensitivity of malformation detection?**

Screening studies conducted on more than 500,000 fetuses have shown that approximately 11,000 were malformed (2.2%). Mean sensitivity of ultrasound in these studies was 45.5% (range, 14%-80%). The lowest values (14%-38%) occurred when screening was performed by examiners who varied in terms of skill and experience. The second highest value (61%) occurred in a collaborative study conducted on more than 170,000 pregnant women--nearly 4000 malformed fetuses were found.

**CONCLUSION**

Ultrasonography, especially when performed routinely--before clinical signs indicate that it might be necessary--can improve pregnancy outcomes. This is particularly true in cases of fetal malformation, as 90% of them do not present with clinical symptoms. In the absence of prenatal diagnosis of malformations, many opportunities for optimal management can be lost, such as failing to look for chromosome aberrations, missing an opportunity to provide maternal transport to tertiary centers, and precluding the termination option in case of severe anomaly. Ultrasonographic screening for malformation should be performed in all gravidas--at least once by expertly trained personnel--at about 20 weeks' gestation. This approach has proved to be both feasible and cost-effective. Also, the psychological benefit of advance knowledge--whether the news is good or bad--is particularly valuable.

**Disclosures:**

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